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EDITORIAL COMMENT

A Song of Pressure and Flow, or There and Back Again*

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It has been more than 2 decades since fractional flow reserve (FFR) was introduced, and it now plays a central role in guidelines for stable coronary artery disease (1,2). FFR is calculated as the ratio of the pressure distal to a stenosis to the pressure proximal to a stenosis during hyperemia. However, FFR's adoption has been slow, with international uptake estimated at <10% (3). Reasons for this may include the costs and practicalities of administering adenosine, patient discomfort during hyperemia, and safety concerns in certain patient subgroups (4).

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In this issue of *JACC: Cardiovascular Interventions*, Mejía-Rentería et al. (5) investigate the diagnostic performance of the "quantitative flow ratio" (QFR), a physiological assessment that, it is hoped, will provide a faster, safer, and cheaper surrogate measure of FFR that does not require passing of a coronary pressure wire or pharmacological hyperemia. The diagnostic performance of QFR has been investigated in small studies previously (6,7). However, because it relies on angiographic flow measurements, Mejía-Rentería et al. wished to investigate whether coronary microcirculatory parameters could affect its accuracy. The investigators now show that QFR's diagnostic performance, when judged against FFR, does degrade in patients with coronary microcirculatory dysfunction, as high microvascular resistance causes the positive predictive value to decrease from 93% to 67%.

The method of QFR calculation used by the investigators requires 2 pieces of information. First, a 3-dimensional model of the stenosis is constructed from 2 angiographic views. Second, the flow velocity in the vessel is measured using simple "frame counting" of contrast. Using these data, the pressure drops over the length of the vessel can be simulated and the QFR calculated.

QFR therefore indirectly estimates coronary pressure ratios by measuring flow, whereas FFR uses direct measurements of coronary pressure. Given this, "fractional flow reserve" may seem a surprising name for a ratio of pressures, and indeed this gives interesting insights into the history of coronary physiology.

CORONARY FLOW MEASUREMENTS AND THE BIRTH OF CORONARY PHYSIOLOGY

Myocardial ischemia in patients with stable angina develops when myocardial oxygen demand exceeds what the coronary circulation can supply. This supply can be thought of as the volume of blood delivered to a tissue per second (cm^3/s) and can be quantified simply by multiplying the blood flow velocity through the vessel (cm/s) by the vessel's cross-sectional area (cm^2).

By the early 1990s, technology had evolved sufficiently to allow velocity sensors to be mounted on angioplasty guidewires (8). By measuring coronary flow velocity at rest, and also during hyperemia, physicians could now estimate a vessel's ability to meet the increased flow requirements during exercise. The ratio of flow velocity during hyperemia to that at rest was termed the coronary flow (velocity)

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reserve (CFR). Observational data showed that using a CFR cutoff of 2.0 provided superior risk stratification in patients with intermediate-severity coronary lesions than single-photon emission computer tomography (9).

THE ERA OF PRESSURE-DERIVED CORONARY PHYSIOLOGY

However, these flow-measuring guidewires could also measure pressure. Initially it was unclear how the pressure throughout the cardiac cycle could be interpreted. As in an electric circuit, pressure (or voltage) = flow (or current) × resistance, so pressure across the cardiac cycle could only become an accurate surrogate for flow if resistance across the coronary circulation were constant. Pijls et al. (10) proposed, however, that during hyperemia, resistance is low and varies minimally. They therefore published a paper covering the experimental basis for a pressure-derived estimate of flow reserve, FFR. More recently, investigators have hypothesized performing pressure measurements during the "wave-free" period of diastole, when resistance is naturally minimal and constant, providing the instantaneous wave-Free Ratio (iFR).

With time, these more practical pressure-based measurements have gained popularity. Not only are the pressure-sensing guidewires cheaper and easier to use than the flow-measuring models, but studies showed that data can be useful for treatment decision making at the stenosis level. The loss in pressure across a stenosis is related to the flow-limiting potential of the lesion (10). This was in contrast to CFR, for which an abnormally low value could represent limitations to flow anywhere along the vessel length, including the distal microcirculation.

The data supporting FFR's use in intermediate coronary stenoses followed over the next 2 decades. The DEFER (11), FAME (12), and FAME-2 (13) studies went on to show the safety of deferring percutaneous coronary intervention in patients with FFRs >0.75 and reduced composite endpoints (largely urgent revascularization) from intervening on lesions with FFRs < 0.80.

As with many other indexes, patients requiring clinical assessment often have values close to the clinical cutoffs of CFR and FFR, and in these patients, recent data show that CFR and FFR discordance occurs in about one-third of patients (14). Interestingly, in these discordant cases, it appears that it is CFR that better categorizes the high-risk patients rather than FFR. This begs the question: is it flow we should be trying to measure in these patients with intermediate stenoses, rather than pressure? Or even both? One might argue that the strength of pressure-derived measurements lies in their ability to identify focal pressure drops over lesions and guide revascularization strategies, whereas CFR seems to provide more accurate information on disease severity and prognostication. Perhaps by combining these 2 measures, patients can be managed to the best of our current evidence base.

A FLOW RENAISSANCE?

At first the results of this new study might appear disappointing. In patients without hemodynamically significant lesions (as judged by FFR) but with high microvascular resistance, QFR gives "false positives." However, is this a fair assessment? Possibly not, and there are 2 reasons we might be optimistic.

First, one could argue that QFR's utility could lie in identifying patients at low risk who do not need to progress to direct FFR measurement with a pressure wire. If so, this study's results are encouraging, with the negative predictive value remaining as high at 87% even in patients with coronary microcirculatory dysfunction.

Second, we must remember that FFR is estimating flow only by measuring pressure, despite its name. Ironically, QFR is now trying to estimate pressure gradients by measuring flow. This may strike the reader as peculiar when one remembers the prognostic importance of CFR in CFR/FFR discordance (14). One therefore has to wonder: in patients with high microvascular resistance and lower coronary blood flow, maybe these "false positives" for QFR are not so false after all?

Conversely, we don't currently know the significance of the rarer "false negative" QFR readings (i.e., patients with FFRs <0.80 but normal QFRs). Hopefully future studies investigating the relationship among QFR, FFR, and CFR will demonstrate whether such cases are truly failures of QFR to identify flow-limiting lesions or instead cases in which CFR is preserved and QFR identifies patients who are at lower risk (14).

We commend the investigators for this study; any new measure should first be validated against the "gold standard" by which patients are currently treated, and FFR, and more recently iFR, have been extensively validated (3). However, the investigators also acknowledge a limitation in having not stratified their results by CFR values. Such an analysis might

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indeed show superiority for QFR over FFR. Indeed, if QFR can accurately measure flow, it will not merely be a less invasive surrogate for FFR but rather synergistic with it, providing us with a fast, practical, safe, and reliable measure of CFR.

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